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L2: Entry 1 of 51 File: PGPB Oct 18, 2007

DOCUMENT-IDENTIFIER: US 20070243203 A1
TITLE: Vaccine for Prevention and Treatment of Hiv-Infection

Brief Summary Text:
[0084] Vaccine preparation is generally described in New Trends and Developments in Vaccines, edited by Voller et al., University Park Press, Baltimore, Md., U.S.A. 1978. Encapsulation within liposomes is described, for example, by Fullerton, U.S. Pat. No. 4,235,877. Conjugation of proteins to macromolecules is disclosed, for example, by Likhite, U.S. Pat. No. 4,372,945 and by Armor et al., U.S. Pat. No. 4,474,757.

Brief Summary Text:
[0100] Such immunostimulants as described above may be formulated together with carriers, such as for example liposomes, oil in water emulsions, and or metallic salts, including aluminium salts (such as aluminium hydroxide). For example, 3D-MPL may be formulated with aluminium hydroxide (EP 0 689 454) or oil in water emulsions (WO 95/17210); QS21 may be advantageously formulated with cholesterol containing liposomes (WO 96/33739), oil in water emulsions (WO 95/17210) or alum (WO 98/15287); CpG may be formulated with alum (Davis et al. supra ; Brazolot-Millan supra) or with other cationic carriers.

Brief Summary Text:
[0101] Combinations of immunostimulants are also preferred, in particular a combination of a monophosphoryl lipid A and a saponin derivative (WO 94/00153; WO 95/17210; WO 96/33739; WO 98/56414; WO 99/12565; WO 99/11241), more particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153. Alternatively, a combination of CpG plus a saponin such as QS21 also forms a potent adjuvant for use in the present invention. Alternatively the saponin may be formulated in a liposome or in an Iscorn and combined with an immunostimulatory oligonucleotide.

Brief Summary Text:
[0102] Thus, suitable adjuvant systems include, for example, a combination of monophosphoryl lipid A, preferably 3D-MPL, together with an aluminium salt. An enhanced system involves the combination of a monophosphoryl lipid A and a saponin derivative particularly the combination of QS21 and 3D-MPL as disclosed in WO 94/00153, or a less reactogenic composition where the QS21 is quenched in cholesterol containing liposomes (DQ) as disclosed in WO 96/33739. This combination may additionally comprise an immunostimulatory oligonucleotide.

Brief Summary Text:
[0106] Particularly preferred adjuvant combinations for use in the formulations according to the invention are as follows: [0107] i) 3D-MPL+QS21 in a liposome [0108] ii) Alum+3D-MPL [0109] iii) Alum+QS21 in a liposome+3D-MPL [0110] iv) Alum+CpG [0111] v) 3D-MPL+QS21+oil in water emulsion [0112] vi) CpG

Description of Disclosure:
[0336] To prepare Adjuvant formulation 1 B, A mixture of lipid (such as phosphatidylcholine either from egg-yolk or synthetic) and cholesterol and 3 D- MPL in organic solvent, is dried down under vacuum (or alternatively under a stream of inert gas). An aqueous solution (such as phosphate buffered saline) is then added,

and the vessel agitated until all the lipid is in suspension. This suspension is then microfluidised until the liposome size is reduced to about 100 nm, and then sterile filtered through a 0.2 .mu.m filter. Extrusion or sonication could replace this step.

Description of Disclosure:
[0338] The liposomes have a defined size of 100 nm and are referred to as SUV (for small unilamelar vesicles). If this solution is repeatedly frozen and thawed the vesicles fuse to form large multilamellar structures (MLV) of size ranging from 500 nm to 15 .mu.m. The liposomes by themselves are stable over time and have no fusogenic capacity.

Description of Disclosure:
[0339] QS21 in aqueous solution is added to the liposomes to reach a final 3 D- MPL and QS21 concentrations of 100 .mu.g/ml.

Description of Disclosure:
[0344] F4Q not codon optimized, purified according to purification method I, was diluted in a phosphate/Arginine buffer pH 6.8. The dilution was mixed with two different concentrated adjuvants (adjuvants 2A and 1B) in order to obtain a final formulation of 40 .mu.g/dose of 500 .mu.l of F4 in presence of 290 (for adjuvant 2A)--300 (for adjuvant 1B) mM Argnine, 50 .mu.g MPL and 50 .mu.g QS21. 100 .mu.l of each formulation were injected in mice.

Description of Disclosure:
[0347] Total antibody responses were characterised by ELISAs specific for p24, p17, RT, Nef and F4. The following table, Table 2, summarises where antigen specific humoral responses were observed in each strain. The results indicate the presence or absence of antibodies compared to control animals immunized with adjuant alone. The results presented are a compilation from two separate but identical experiments. In the table, 2A refers to antigen formulated with 3D-MPL and QS21 in an oil in water emulsion and 1B refers to antigen formulated with 3D-MPL, QS21 and cholesterol containing liposomes. TABLE-US-00028 TABLE 2 mouse strain p17 p24 Nef RT F4 CB6F1 +/- + + + + +2A -1B Balb/c - + + + + +/-2A -1B C3H - - - - - DBA - + + + + CBA - - +/- + + +2A -1B +2A +/-1B 129Sv - + + + + B6D2F1 +/- + + + + +2A -1B OF1 + + + + + + = presence of antibodies - = absence of antibodies

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L2: Entry 2 of 51 File: PGPB Oct 4, 2007

DOCUMENT-IDENTIFIER: US 20070232537 A1
TITLE: INTRANASAL PYY FORMULATIONS WITH IMPROVED TRANSMUCOSAL PHARMACOKINETICS

Description of Disclosure:
[0009] FIG. 1: Concentration versus time curves for plasma pharmacokinetics in male rabbits for intranasal PYY with various formulations containing either a poly-ionogenic buffer salt or a buffer salt having a net single ionogenic moiety. The formulations contained 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA, 25 mM lactose, 100 mM sorbitol, and 0.5% chlorobutanol, along with either 10 mM citrate buffer (pH 5.0) (circle symbols), 10 mM acetate buffer (pH 4.0) (square symbols), 10 mM lactate buffer (pH 4.0) (triangle symbols), or 10 mM arginine buffer (pH 4.0) (diamond symbols).

Description of Disclosure:
[0014] The foregoing mucosal Y2 receptor-binding peptide formulations and preparative and delivery methods of the invention provide improved mucosal delivery of a Y2 receptor-binding peptide to mammalian subjects. These compositions and methods can involve combinatorial formulation or coordinate administration of one or more Y2 receptor-binding peptides with one or more mucosal delivery-enhancing agents. Among the mucosal delivery-enhancing agents to be selected from to achieve these formulations and methods are (A) solubilization agents; (B) charge modifying agents; (C) pH control agents; (D) degradative enzyme inhibitors; (E) mucolytic or mucus clearing agents; (F) ciliostatic agents; (G) membrane penetration-enhancing agents (e.g., (i) a surfactant, (ii) a bile salt, (iii) a phospholipid or fatty acid additive, mixed micelle, liposome, or carrier, (iv) an alcohol, (v) an enamine, (iv) an NO donor compound, (vii) a long-chain amphipathic molecule (viii) a small hydrophobic penetration enhancer; (ix) sodium or a salicylic acid derivative; (x) a glycerol ester of acetoacetic acid (xi) a cyclodextrin or beta-cyclodextrin derivative, (xii) a medium-chain fatty acid, (xiii) a chelating agent, (xiv) an amino acid or salt thereof, (xv) an N-acetylamino acid or salt thereof, (xvi) an enzyme degradative to a selected membrane component, (xvii) an inhibitor of fatty acid synthesis, (xviii) an inhibitor of cholesterol synthesis; or (xiv) any combination of the membrane penetration enhancing agents of (i)-(xviii)); (H) modulatory agents of epithelial junction physiology, such as nitric oxide (NO) stimulators, chitosan, and chitosan derivatives; (I) vasodilator agents; (J) selective transport-enhancing agents; and (K) stabilizing delivery vehicles, carriers, supports or complex-forming species with which the Y2 receptor-binding peptide(s) is/are effectively combined, associated, contained, encapsulated or bound to stabilize the active agent for enhanced mucosal delivery.

Description of Disclosure:
[0076] Within more detailed aspects of the invention, one or more membrane penetration-enhancing agents may be employed within a mucosal delivery method or formulation of the invention to enhance mucosal delivery of Y2 receptor-binding peptide proteins, analogs and mimetics, and other biologically active agents disclosed herein. Membrane penetration enhancing agents in this context can be selected from: (i) a surfactant; (ii) a bile salt; (iii) a phospholipid additive, mixed micelle, liposome, or carrier; (iv) an alcohol; (v) an enamine; (vi) an NO donor compound; (vii) a long-chain amphipathic molecule; (viii) a small hydrophobic penetration enhancer; (ix) sodium or a salicylic acid derivative; (x) a glycerol

ester of acetoacetic acid; (xi) a cyclodextrin or beta-cyclodextrin derivative; (xii) a medium-chain fatty acid; (xiii) a chelating agent; (xiv) an amino acid or salt thereof; (xv) an N-acetylamino acid or salt thereof, (xvi) an enzyme degradative to a selected membrane component; (xvii) an inhibitor of fatty acid synthesis, or (xviii) an inhibitor of cholesterol synthesis; or (xix) any combination of the membrane penetration enhancing agents recited in (i)-(xviii) above.

Description of Disclosure:
[0210] The results of Examples 13 and 14 indicate that PYY stability is dramatically improved by decreasing formulation pH to approximately 4 and/or exchanging the poly-ionogenic citrate salt buffer for a buffer salt species having a net single ionogenic moiety. In light of this improved stability, an in vitro permeation assay was performed to compare the relative degree of PYY permeation of formulations containing a buffer salt with a net single ionogenic moiety (mono-ionogenic) to formulations containing a poly-ionogenic buffer salt. Table 17 below describes the four PYY formulations assessed for percent PYY permeation using normal, human-derived tracheal/bronchial epithelial cells (EpiAirway.TM. Tissue Model System). Each formulation contained the low molecular weight excipients 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA and 25 mM lactose, 100 mM sorbitol, 5 mg/mL chlorobutanol, 10 mM poly-ionogenic (pH 5) or mono-ionogenic buffer salt (pH 4) and 1 or 2 mg/mL PYY. The mono-ionogenic buffer salts are comprised of acetate, lactate and arginine. Citrate was used as a poly-ionogenic salt buffer PYY permeation control. Refer to Example 2 for details of the PYY permeation protocol. For the purposes of the instant example, the buffer salt listed in the "Buffer Salt Formulation" column of Table 17 will be used to refer to the entire formulation composition (e.g., the "citrate" formulation describes the formulation comprising PYY with M-.beta.-CD, DDPC, EDTA and citrate buffer salt). TABLE-US-00017 TABLE 17 PYY Formulations Comprising Low Molecular Weight Excipients with a Buffer Salt Ionic Buffer Salt PYY Species Formulation (mg/mL) Formulation Poly- Citrate 1-2 45 mg/mL M-.beta.-CD, 1 mg/mL ionogenic DDPC, 1 mg/mL EDTA, 10 mM citrate buffer (pH 5.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Mono- Acetate 1-2 45 mg/mL M-.beta.-CD, 1 mg/mL ionogenic DDPC, 1 mg/mL EDTA, 10 mM acetate buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Lactate 1-2 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA, 10 mM lactate buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Arginine 1-2 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA, 10 mM arginine buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB

Description of Disclosure:
[0218] Four intranasal formulations of PYY were evaluated in the study. The vehicle composition for each formulation is provided in Table 20. Each formulation contained the low molecular weight excipients 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA and 25 mM lactose, 100 mM sorbitol, 5 mg/mL chlorobutanol, 10 mM poly-ionogenic (pH 5) or mono-ionogenic buffer salt (pH 4) and 13.57 mg/mL PYY. The mono-ionogenic buffer salts were acetate, lactate and arginine. Citrate was used as a poly-ionogenic salt buffer. For the purposes of the instant example, the buffer salt listed in the "Buffer Salt" column of Table 20 will be used to refer to the entire formulation composition (e.g., the "citrate" formulation describes the formulation comprising PYY with M-.beta.-CD, DDPC, EDTA and citrate buffer salt). TABLE-US-00020 TABLE 20 Composition of PYY Formulations Ionic Buffer PYY Species Salt Group (mg/mL) Formulation Poly- Citrate 1 13.67 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL ionogic EDTA, 10 mM citrate buffer (pH 5.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Mono- Acetate 2 13.67 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL ionogenic EDTA, 10 mM acetate buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Lactate 3 13.67 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA, 10 mM lactate buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB Arginine 4 13.67 45 mg/mL M-.beta.-CD, 1 mg/mL DDPC, 1 mg/mL EDTA, 10 mM arginine buffer (pH 4.0), 25 mM lactose, 100 mM sorbitol, 0.5% CB

Description of Disclosure:

[0237] There was a trend towards increased absorption for the arginine and acetate buffer systems based on bioavailability comparisons to the citrate buffer formulation.

Description of Disclosure:
[0238] The pharmacokinetic study compared the bioavailability of different salt buffered systems. The bioavailability increased with both the acetate and arginine buffered systems compared to the citrate and lactate buffered systems, but there was no statistical significance across all groups. The variability is decreased by at least a factor of 2 for the arginine buffer compared to all other buffer systems.

Description of Disclosure:
[0239] The data in Table 22 (also graphically presented in FIG. 1) shows that all formulations had similar T.sub.max values indicating that net valence of the buffer salt had no effect on the time to maximum observed concentration of PYY in the blood. In comparing C.sub.max and AUC, Group 4 represented by the formulation containing the mono-ionogenic lactate buffer salt performed similarly to the formulation with the poly-ionogenic citrate buffer salt (Group 1). However, the formulations with the mono-ionogenic arginine buffer salt (Group 3) and acetate buffer salt (Group 2) had higher C.sub.max and AUC values compared to the formulation with the poly-ionogenic citrate buffer salt (Group 1). Specifically, the formulations with either an arginine or an acetate buffer salt increased C.sub.max 54% and 45%, respectively, over that of the formulation with the poly-ionogenic citrate buffer salt. Further, both the formulations with mono-ionogenic buffers salts, arginine and acetate, also increased AUC values 42% and 50%, respectively, above that of the formulation with the poly-ionogenic citrate buffer salt.

Description of Disclosure:
[0240] These data show the surprising and unexpected discovery that exchanging the poly-ionogenic citrate salt buffer for a mono-ionogenic buffer salt species, for example arginine or acetate, in a formulation with low molecular weight excipient improves PYY bioavailability nearly two-fold. Further, the intersubject comparison of the pharmacokinetic parameters indicates that the use of the arginine buffer salt markedly decreases intersubeject variability indicating the use of the buffer salt arginine in a pharmaceutical formulation would reduce the necessity of determining the specific therapeutically effective dose range of individual patients.

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(liposome same nsaid) and phosphatidylcholine	13

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L5	(liposome same nsaid) and phosphatidylcholine	13	L5
L4	liposome same nsaid same phosphatidylcholine	2	L4
L3	liposome same nsaid	114	L3
L2	L1 and liposome	51	L2
L1	arginine adj3 buffer	283	L1

END OF SEARCH HISTORY

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L7	L4 and 424/450.ccls.	31	L7
L6	liposome adj15 (benzyl adj1 alcohol)	2	L6
L5	liposome adj10 (benzyl adj1 alcohol)	2	L5
L4	liposome same (benzyl adj1 alcohol)	1180	L4
L3	L2 and 424/450.ccls.	5	L3
L2	liposome same phenol same stabili$	117	L2
L1	liposome adj10 phenol	28	L1

END OF SEARCH HISTORY

L7: Entry 30 of 31 File: USPT Jan 30, 1990

DOCUMENT-IDENTIFIER: US 4897269 A
TITLE: Administration of drugs with multiphase liposomal delivery system

Detailed Description Paragraph Table (9):

Materials

Minoxidil Milled 2 g Butylated Hydroxyanisole USP (BHA) 25 mg Ethanol USP (95%) 50 ml Propylene Glycol USP 35 ml Benzyl Alcohol NF* 4.5 ml Stock Solution (CaCl.sub.2 8 mM solution) 415 ml Tween 80** 5.0 ml

*Not to be added to the 2% minoxidil liposome formulation without preservatives. * & **If Tween 80 and/or benzoyl alcohol are used they displace an equivalent volume of CaCl.sub.2 solution.

Current US Original Classification (1):
424/450